# Constructing chiral bicyclo[3.2.1]octanes via palladium-catalyzed asymmetric tandem Heck/carbonylation desymmetrization of cyclopentenes

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Transition-metal-catalyzed tandem Heck/carbonylation reaction has emerged as a powerful tool for the synthesis of structurally diverse carbonyl molecules, as well as natural products and pharmaceuticals. However, the asymmetric version was rarely reported, and remains a challenging topic. Herein, we describe a palladium-catalyzed asymmetric tandem Heck/carbonylation desymmetrization of cyclopentenes. Alcohols, phenols and amines are employed as versatile coupling reagents for the construction of multifunctional chiral bicyclo [3.2.1]octanes with one all-carbon quaternary and two tertiary carbon stereogenic centers in high diastereo- and enantioselectivities. This study represents an important progress in both the asymmetric tandem Heck/carbonylation reactions and enantioselective difunctionalization of internal alkenes.

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Transition-metal (TM)-catalyzed carbonylation reaction[1–16], especially palladium-catalyzed tandem Heck/carbonylation reaction, presents an efficient method to construct a variety of synthetically versatile carbonyl compounds from readily accessible organic halides and alkenes[17–21]. Moreover, these methods have been applied as key steps in the total synthesis of natural products and bioactive molecules[22–28]. Very recently, Reisman and co-workers realized the total synthesis of (+)-Perseanol employing palladium-catalyzed tandem Heck/carbonylation to assemble the vital tetracyclic core (Fig. 1a)[29]. However, the asymmetric version of tandem Heck/carbonylation reactions was rare, and remains a challenging topic. Some inherent issues, such as the strong π-acidity and coordination ability of CO, would hamper the oxidative addition of organohalides towards low-valent metal species[30]. In addition, the harsh reaction conditions (high temperature and high CO pressure), the incidental racemization[31], the β-hydrogen elimination of alkylpalladium intermediates, the direct carbonylation of organohalides, and other competitive side-reactions make the asymmetric progress more difficult and complicated. Recently, three representative works on palladium-catalyzed asymmetric tandem Heck/carbonylation reaction of 1,1-disubstitueted alkenes to synthesize dihydrobenzofurans, oxindole derivatives, and 3,4-dihydroisoquinolines have been realized by Correia's group[32], Zhu and Luo's group[33], and Zhang's group[34], respectively. In contrast to the success of 1,1-disubstituted alkenes (the alkylpalladium intermediates lack eliminable β-hydrogen), the TM-catalyzed asymmetric tandem Heck/carbonylation reaction of unactivated internal alkenes has not been developed until now.

On the other hand, bicyclo[3.2.1]octanes are found in several natural products with antibacterial, antioxidant, antithrombosis, and antitumor activities[35,36]. However, constructing such intricate polycyclic bridge ring compounds with multiple chiral centers simultaneous implementation remains a challenging project[37–46]. Based on our research interest in Heck reactions[47–50], herein, we describe a palladium-catalyzed asymmetric tandem Heck/carbonylation desymmetrization of cyclopentenes to construct multifunctional chiral bicyclo[3.2.1]octanes bearing one all-carbon quaternary and two tertiary carbon stereogenic centers in excellent diastereoselectivities and enantioselectivities (Fig. 1b). Suppressing the foreseeable side reactions, such as β-hydrogen elimination of alkylpalladium intermediates, and the direct CO insertion or nucleophiles insertion reaction (Fig. 1c), is the key to the success of this reaction.

## Results

**Reaction optimization.** After systematic evaluation of the reaction conditions, the desired chiral bicyclo[3.2.1]octane product **3aa** was achieved in 81% yield and 96% ee employing $Pd_2dba_3 \cdot CHCl_3$ (5 mol%) as the catalyst, (S)-Difluorphos **L1** (20 mol%) as the ligand, $K_2CO_3$ (2 equiv) as the base, and mixed 1,2-
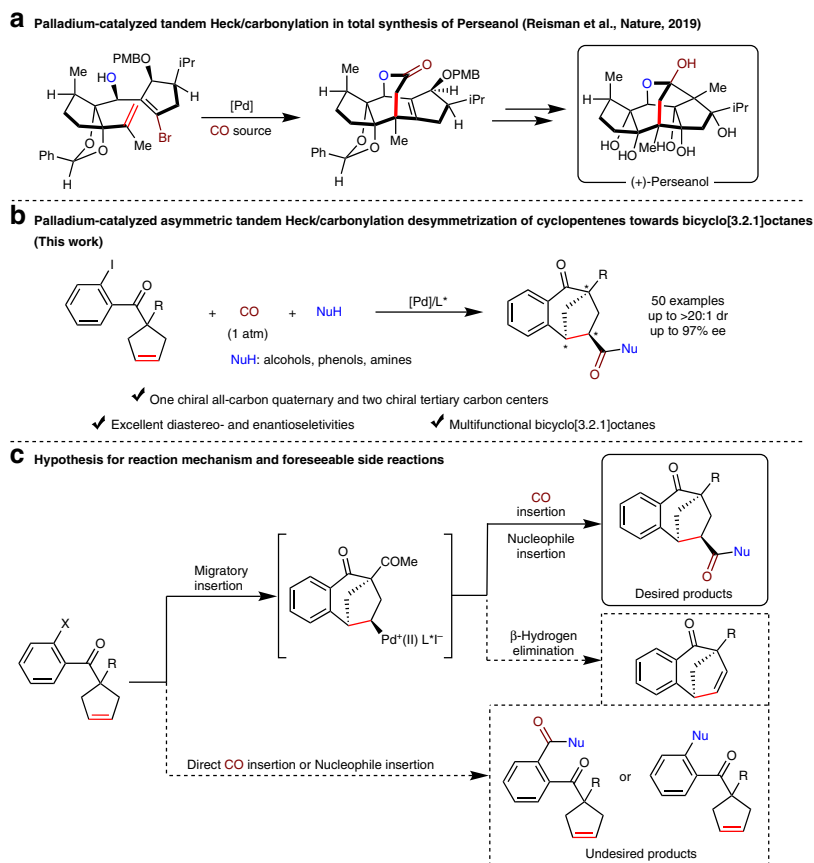


**Fig. 1 Palladium-catalyzed tandem Heck/carbonylation reactions of alkenes. a** Pd-catalyzed tandem Heck/carbonylation as key step to the total synthesis of (+)-Perseanol. **b** Palladium-catalyzed asymmetric tandem Heck/carbonylation of internal alkenes towards bicyclo[3.2.1]octanes (this work). **c** Hypothesis of mechanism for the tandem Heck/carbonylation reaction and foreseeable side reactions.

**Table 1 Optimization of reaction conditions[a].**
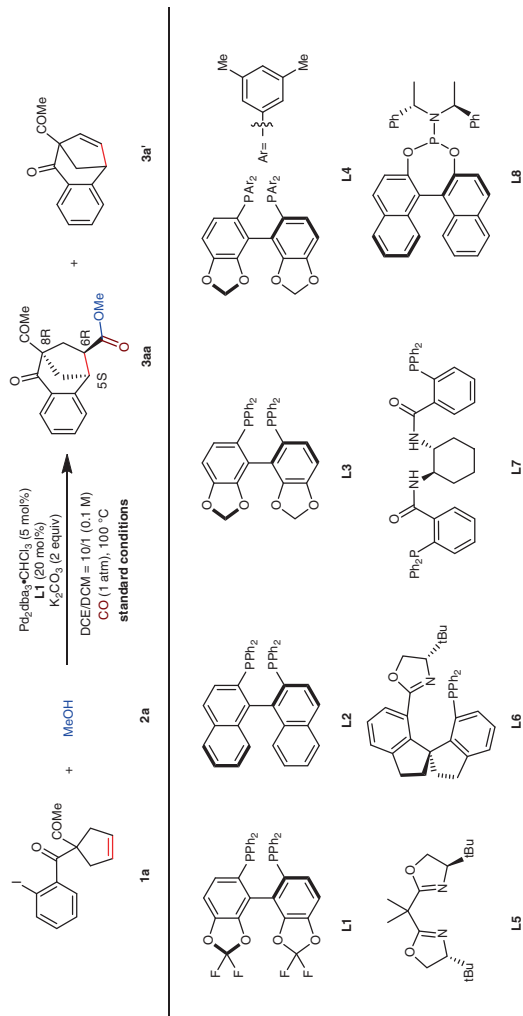


| Entry | Deviation of standard conditions | Yield of 3aa (%)[b] | Dr of 3aa[c] | Ee of 3aa (%)[d] | Yield of 3a' (%)[b] |
|---|---|---|---|---|---|
| 1 | None | 81 | >20:1 | 96 | <2 |
| 2 | Pd(OAc)$_2$ instead of Pd$_2$dba$_3$·CHCl$_3$ | 71 | >20:1 | 66 | 6 |
| 3 | Pd$_2$dba$_3$ instead of Pd$_2$dba$_3$·CHCl$_3$ | 31 | >20:1 | 85 | 7 |
| 4 | L2 instead of L1 | 82 | >20:1 | 52 | <2 |
| 5 | L3 instead of L1 | 75 | 15:1 | 79 | 9 |
| 6 | L4 instead of L1 | 60 | >20:1 | 80 | <2 |
| 7 | L5 instead of L1 | 59 | >20:1 | −5 | <2 |
| 8 | L6 instead of L1 | 21 | >20:1 | 5 | <2 |
| 9 | L7 instead of L1 | <2 | - | - | 13 |
| 10 | L8 instead of L1 | <2 | - | - | 21 |
| 11 | 10 mol% of L1 instead of 20 mol% of L1 | 63 | 11:1 | 36 | 24 |
| 12 | KHCO$_3$ instead of K$_2$CO$_3$ | 57 | 4:1 | 80 | <2 |
| 13 | Na$_2$CO$_3$ instead of K$_2$CO$_3$ | 32 | 7:1 | 53 | <2 |
| 14 | AgOAc instead of K$_2$CO$_3$ | <2 | - | - | 83 |
| 15 | DCE instead of DCE/DCM | 78 | 4:1 | 80 | <2 |
| 16 | DCM instead of DCE/DCM | 75 | >20:1 | 88 | <2 |
| 17 | Toluene instead of DCE/DCM | 69 | 5:1 | 53 | <2 |
| 18 | CH$_3$CN instead of DCE/DCM | 90 | 8:1 | 77 | <2 |
| 19 | DCE/DCM = 1/1 instead of 10/1 | 71 | 10:1 | 96 | 8 |
| 20 | DCE/DCM = 1/10 instead of 10/1 | 38 | 12:1 | 93 | 38 |
| 21 | 80 °C instead of 100 °C | 71 | >20:1 | 77 | <2 |
| 22 | 120 °C instead of 100 °C | 38 | 13:1 | 94 | <2 |

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (1 mmol), [Pd] (10 mol%), ligand (20 mol%), base (0.2 mmol) in 1 mL solvent, 100 °C, 36 h, under CO (1 atm).
[b]Isolated yield.
[c]Determined by ^{1}H NMR analysis.
[d]Determined by HPLC analysis on a chiral stationary phase.

dichloroethane (DCE)/dichloromethane (DCM) (10/1) as the solvent at 100 °C (Table 1, entry 1). Other catalysts, such as Pd(OAc)₂ and Pd₂(dba)₃ were less effective (entries 2 and 3). BINAP **L2**, SEGPHOS **L3**, DM-SEGPHOS **L4** offered **3aa** in 52–80% ee (entries 4–6), while BOX-type ligand **L5**, PHOX-type ligand **L6**, bis(phosphine-amide) ligand **L7** and phosphoramidite ligand **L8** caused the reaction inactivation (entries 7–10). Decreasing the amount of ligand resulted **3aa** in diminished yield, diastereo- and enantioselectivity (entry 11). Screening the additives revealed that K₂CO₃ was optimal, and AgOAc delivered racemic **3a'** in 83% yield, which was formed via β-hydrogen elimination (entries 1 and 12–14). The choice of solvent, also the ratio of the mixed solvent, was crucial to the reaction efficiency (entries 15–20). Adjusting the reaction temperature was inconducive to improve the outcome of the reaction (entries 21–22). The structure and absolute configuration of **3aa** were confirmed by single-crystal X-ray diffraction analysis (see the Supplementary Note 3 for details).

**Substrate scope**. With the optimized reaction conditions in hand, we then tested the substrate scope of alcohols in this asymmetric Heck/carbonylation reaction, and the results were summarized in Fig. 2. Simple primary alcohols, such as ethanol, *n*-propanol and benzyl alcohol afforded the products **3aa–ad** in moderate to good

yields with high enantioselectivities. It is noted that aryl bromine derivative was also a good candidate, delivering **3ab** in 50% yield with 94% ee after prolonging the time to 48 h. Besides, other primary alcohols with various functional groups, such as alkenyl, trifluoromethyl, halogen, trimethylsilyl, even highly sterically hindered adamantly group, all performed well, offering **3ae–ai** in 88–96% ee. Cyclic and acyclic secondary alcohols delivered the corresponding products **3aj–ao** in good efficiency. Products **3ba–da** with different substituents on the benzene ring were produced in good yields with high enantioselectivities. Product **3eb** with two ester groups was achieved in 68% yield with 95% ee.

Phenol esters are important skeletons in pharmaceuticals and bioactive compounds. Although phenols as nucleophilic reagents have been employed in some carbonylation reactions[51,52], they have not met with the success in asymmetric tandem Heck/carbonylation reactions, because the two potential nucleophilic sites at O and C of phenols would increase the complexity of the reaction. Herein, phenols as versatile components were performed in our asymmetric Heck/carbonylation reactions with KHCO₃ as the base and toluene as the solvent (Fig. 3). Electron donating groups (−Me, −*t*Bu, and −OMe), a halogen group (−Cl), an electron withdrawing group (−COMe), as well as a phenyl group at the *para*-position of phenols offered the corresponding products **5aa–ag** in 91–95% ee. *meta*-Chlorine
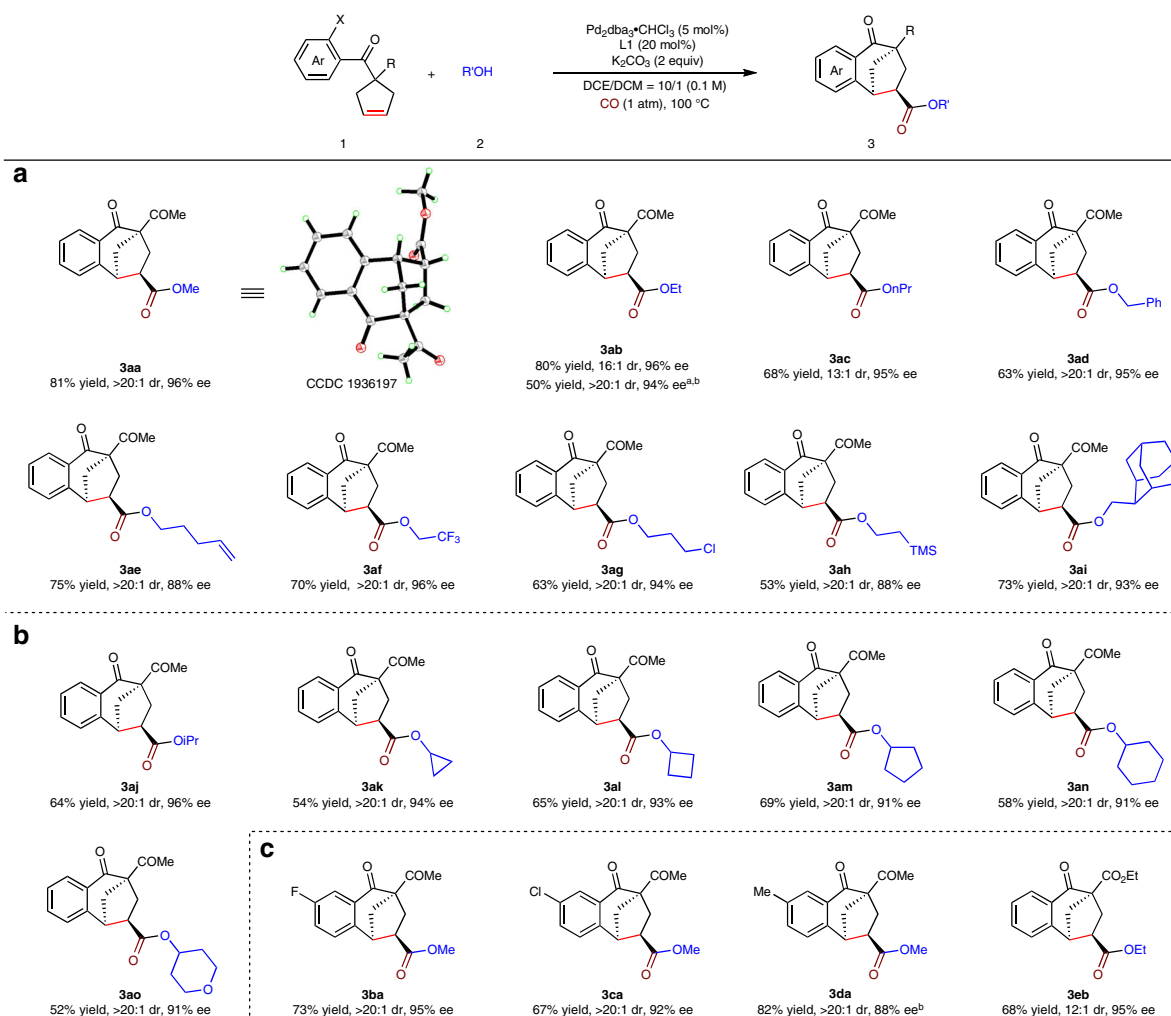


**Fig. 2 Substrate scope. a** Substrate scope of primary alcohols. **b** Substrate scope of secondary alcohols. **c** Substrate scope of the benzoylcyclopentenes. Reaction conditions: X = I, **1** (0.1 mmol), **2** (1 mmol), Pd₂dba₃•CHCl₃ (5 mol%), **L1** (20 mol%), K₂CO₃ (0.2 mmol) in 1 mL solvent, 100 °C, 36 h, under CO (1 atm). Yields of isolated products are given. The dr values were determined by ¹H NMR analysis. The ee values were determined by HPLC analysis on a chiral stationary phase. [a]X = Br. [b]48 h.
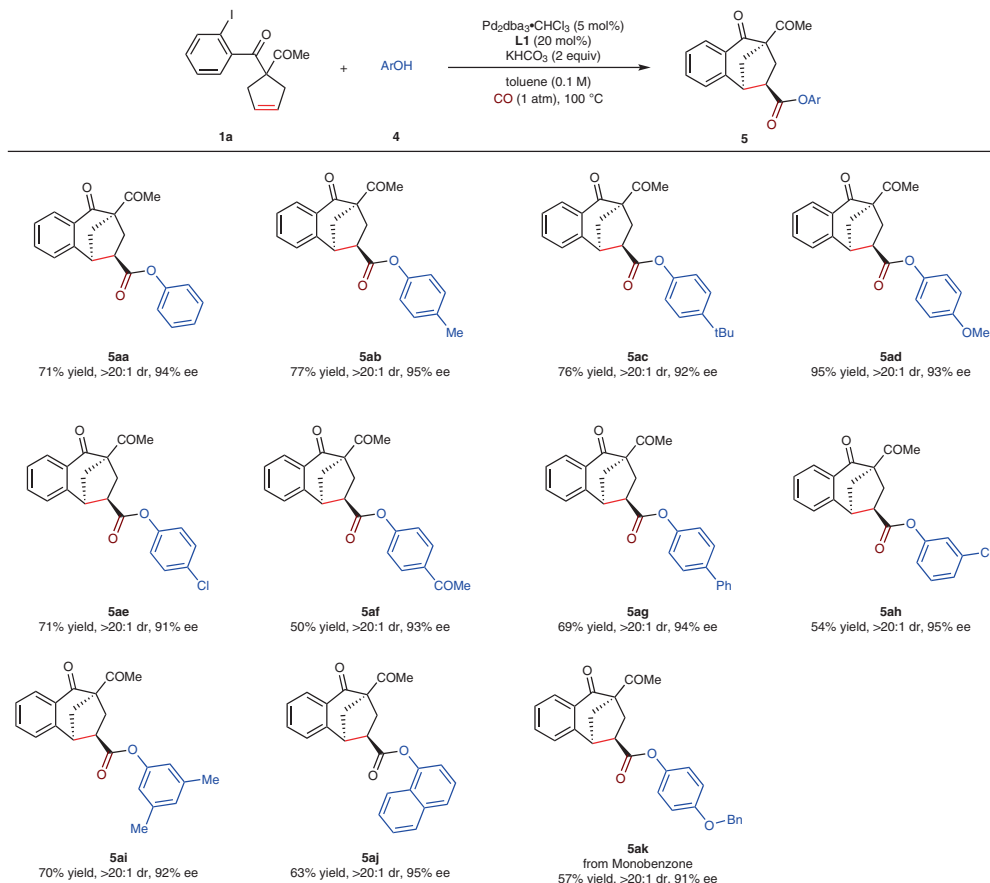
**Fig. 3 Substrate scope of phenols.** Reaction conditions: **1a** (0.1 mmol), **4** (0.25 mmol), Pd₂dba₃•CHCl₃ (5 mol%), **L1** (20 mol%), KHCO₃ (0.2 mmol) in toluene (1 mL), 100 °C, 36 h, under CO (1 atm). Yields of isolated products are given. The dr values were determined by ¹H NMR analysis. The ee values were determined by HPLC analysis on a chiral stationary phase.

substituted phenol **4h** and 3,5-dimethylphenol **4i** could also fulfill the reaction well, and no significant steric hindrance effect was observed. 1-Naphthol delivered **5aj** in 95% ee. Moreover, monobenzone, as a potent skin lightener drug, could give the adduct **5ak** in 91% ee.

To further exhibit the robustness and generality of this reaction, scope of nitrogen nucleophiles was investigated with Pddba₂ (10 mol%) as the catalyst, **L1** (20 mol%) as the ligand, K₂HPO₄ (0.2 mmol) as the base in CH₃CN (1 mL) at 100 °C (Fig. 4). Acyclic secondary alkylamines, such as diethylamine and dibenzylamine delivered products **7aa** (see the Supplementary Note 4 for details on the X-ray crystal structure) and **7ab** in 93 and 94% ee. Cyclic secondary alkylamines furnished products **7ac–ag** in 92–94% ee. Alkylarylamines, such as *N*-methylaniline and indoline, provided **7ah** and **7ai** in 92 and 91% ee. Primary alkylamines, such as *n*-propylamine, benzylamines, and thiophenylmethanamine offered products **7aj–am** in 92–94% ee. Primary arylamines were also qualified to work in this reaction, delivering products **7an–ap** in good enantioselectivities with KHCO₃ as the base after prolonging the reaction time to 48 h. 5-OMe-substituted cyclopentene **1f** performed smoothly to give **7fb** in 97% ee. Finally, pharmaceuticals including Vortioxetine, Trimetazidine and Riluzole were all well late-stage functionalized with bicyclo[3.2.1]octanes to offer **7aq–as** in 88–95% ee.

**Further study**. The enantiodivergent synthesis of (5*R*, 6*S*, 8*S*)-**5ac′** was also realized in 70% yield and 97% ee employing (*R*)-Difluorphos as the ligand (Fig. 5a). To demonstrate the mechanism of this reaction, study on nonlinear effect of the

enantioselectivity of **5ac** was carried out (Fig. 5b). The linear correlation ($R^2 = 0.99$) between the enantioselectivities of the product **5ac** and the enantiopurities of the ligand **L1** revealed the involvement of one active catalyst species in the stereo-determining transition states of the migratory insertion process. On the basis of the above-mentioned results and previous literatures[31,32,47], a proposed mechanism of this reaction is figured in Fig. 5c. Firstly, oxidative addition of the active palladium catalyst with **1a** delivers the cationic Pd(II) intermediate **I**. Intramolecular *syn*-migratory insertion of **I** results in the alkyl-palladium intermediate **II**, which followed by the insertion of CO delivers the intermediate **III**. Finally, the nucleophile insertion of the phenol **4c** to the intermediate **III** produces the product **5ac**. It is noted that the high diastereoselectivity was arisen from the stereospecific *syn*-migratory insertion step, which has been confirmed in our previous work by the deuterium-labeling experiments[47]. The observed stereochemical outcome of the reaction with the C2-symmetric, (*S*)-configured ligand **L1** can be rationalized based on the two diastereomeric intermediates **A1** and **B1** (Fig. 5d). The transition state **B1** is notable for the severe steric repulsion between the benzoyl moiety of the cyclopentene **1a** and the benzene ring of the ligand **L1**, a factor which is not present in the transition state **A1**; this may account for the predominance of the (5*S*, 6*R*, 8*R*) enantiomer of **5ac** in the product.

## Discussion

In summary, we have developed a Pd-catalyzed asymmetric tandem Heck/carbonylation desymmetrization of cyclopentenes. Various bicyclo[3.2.1]octanes bearing one chiral all-carbon
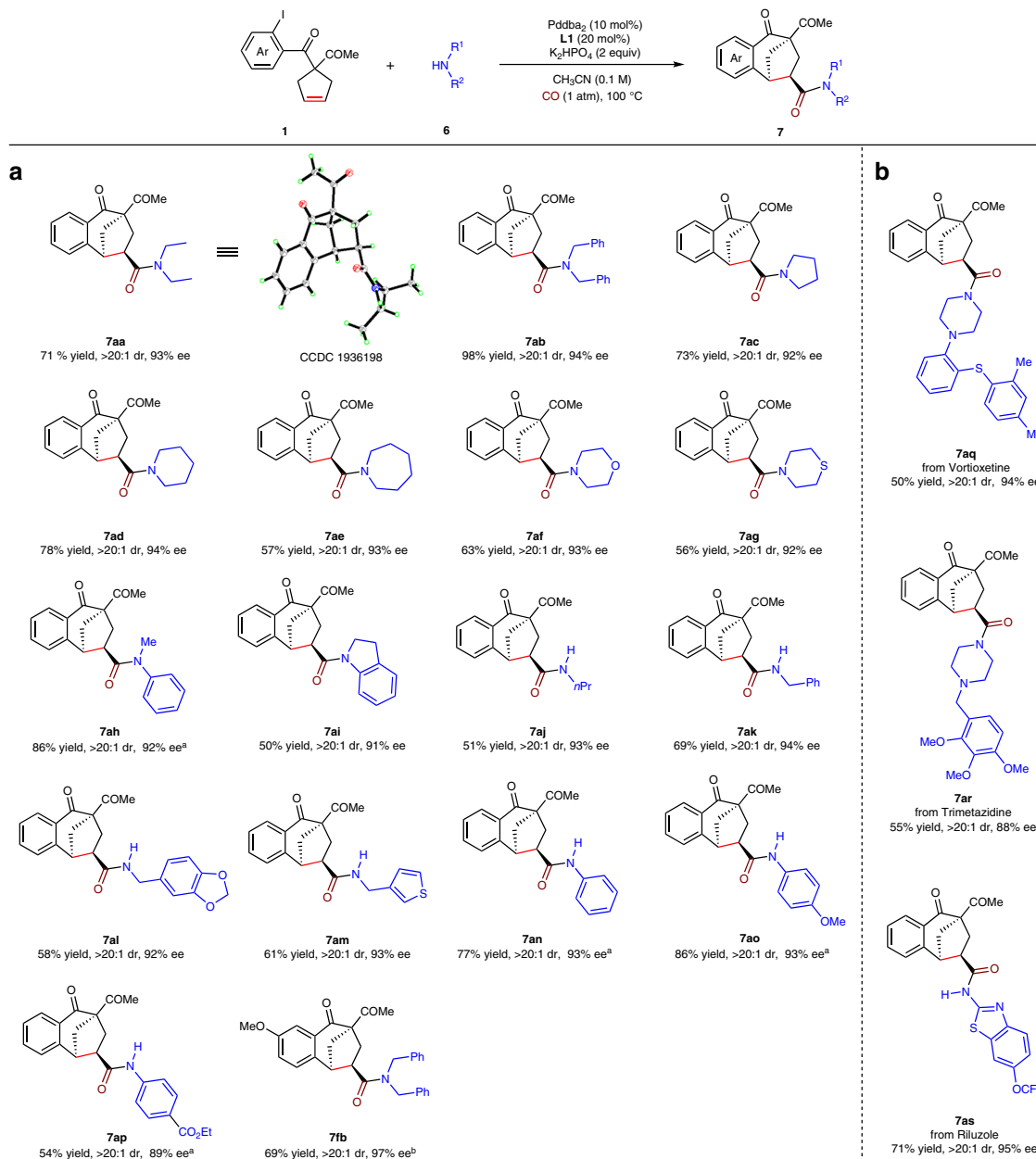
**Fig. 4 Substrate scope. a** Substrate scope of amines. **b** Application to asymmetric late-stage functionalization of pharmaceuticals. Reaction conditions: **1a** (0.1 mmol), **6** (0.2 mmol), Pddba₂ (10 mol%), **L1** (20 mol%), K₂HPO₄ (0.2 mmol) in CH₃CN (1 mL), 100 °C, 36 h, under CO (1 atm). Yields of isolated products are given. The dr values were determined by ¹H NMR analysis. The ee values were determined by HPLC analysis on a chiral stationary phase. [a]K₂HPO₄ was replaced by KHCO₃, 48 h. [b]48 h.

quaternary and two tertiary carbon stereogenic centers were obtained in moderate to good yields with excellent diastereoselectivities and enantiomeric excess. This method provided a general and practical route for the enantioselective difunctionalization of unactivated internal alkenes and chiral bicyclo[3.2.1] octanes.

## Methods

**General procedure for the catalytic reactions with alchohols**. A sealed tube was charged with the cyclopentenes **1** (0.1 mmol, 1 equiv), Pd₂dba₃•CHCl₃ (5 mol%), **L1** (20 mol%), and K₂CO₃ (0.2 mmol, 2 equiv). The vial was thoroughly flushed with CO, and alchohols **2** (1 mmol, 10 equiv), as well as DCE/DCM (10/1, 1 mL) were added under CO atmosphere. The reaction mixture was stirred at 100 °C for 36 h. After the reaction vessel was cooled to room temperature, the solution was concentrated in vacuo and purified by careful chromatography on silica gel (200–300 mesh) (PE/EA = 4/1) to afford the desired products **3**.

**General procedure for the catalytic reactions with phenols**. A sealed tube was charged with the cyclopentenes **1** (0.1 mmol, 1 equiv), phenols **4** (0.25 mmol, 2.5 equiv), Pd₂dba₃•CHCl₃ (5 mol%), **L1** (20 mol%), and KHCO₃ (0.2 mmol, 2 equiv). The vial was thoroughly flushed with CO, and toluene (1 mL) was added under CO atmosphere. The reaction mixture was stirred at 100 °C for 36 h. After the reaction vessel was cooled to room temperature, the solution was concentrated in vacuo and purified by careful chromatography on silica gel (200–300 mesh) (PE/EA = 4/1) to afford the desired products **5**.

**General procedure for the catalytic reactions with amines**. A sealed tube was charged with the cyclopentenes **1** (0.1 mmol, 1 equiv), Pddba₂ (10 mol%), **L1** (20 mol%), and K₂HPO₄ (0.2 mmol, 2 equiv). The vial was thoroughly flushed with CO, and amines **6** (0.2 mmol, 2 equiv), as well as CH₃CN (1 mL) were added under CO atmosphere. The reaction mixture was stirred at 100 °C for 36 h. After the reaction vessel was cooled to room temperature, the solution was concentrated in vacuo and purified by careful chromatography on silica gel (200–300 mesh) (PE/EA = 2/1) to afford the desired products **7**.
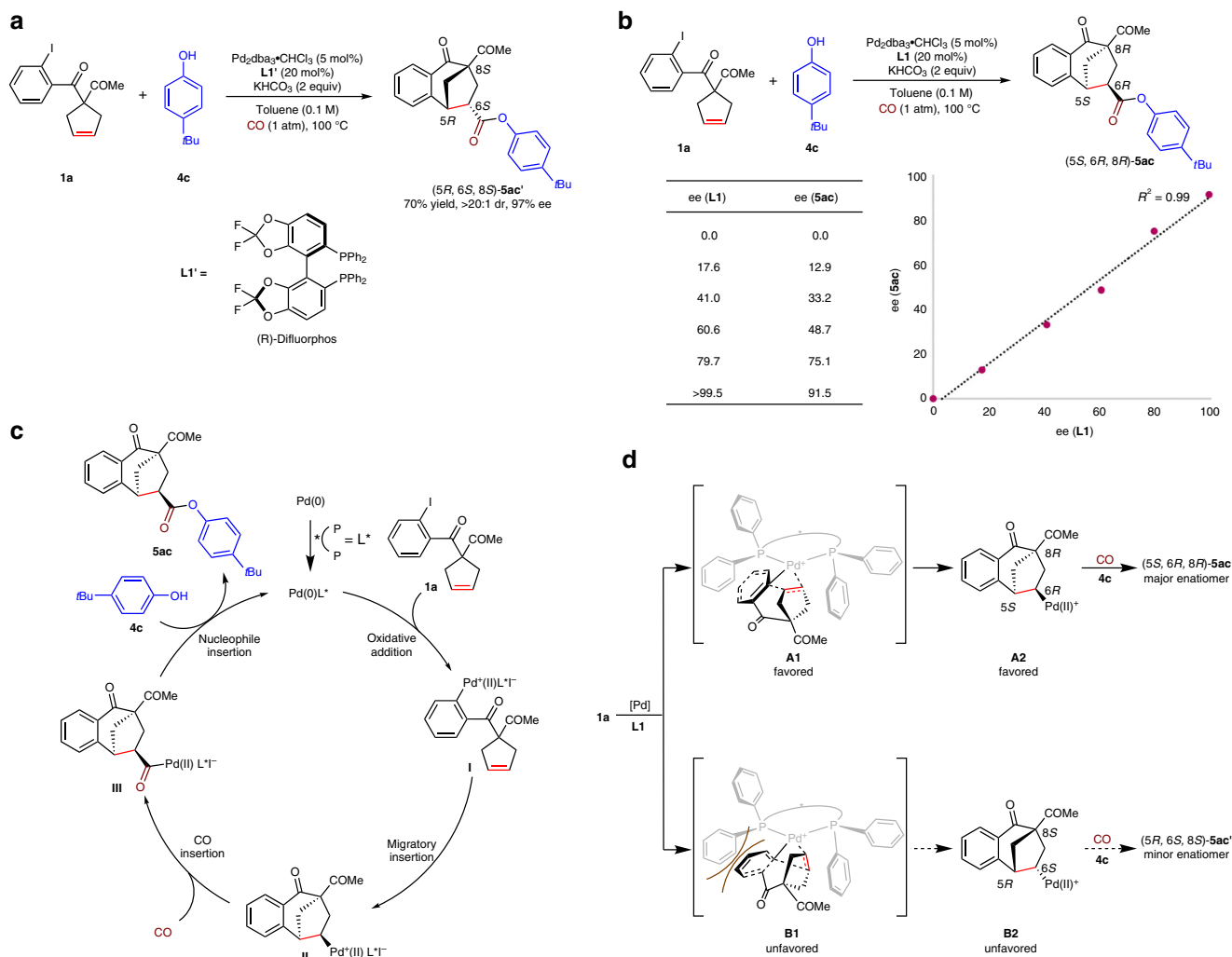
**Fig. 5 Further study on the reaction. a** Enantiodivergent synthesis of (5R, 6S, 8S)-**5ac'**. **b** Linear correlation between the ee values of **5ac** and **L1**. **c** Proposed mechanism. **d** Model for enantioselectivity.

## Data availability

The authors declare that all the data supporting the findings of this study are available within the article and Supplementary Information files, and are also available from the corresponding author upon reasonable request. The X-ray crystallographic coordinates for structures reported in this article have been deposited at the Cambridge Crystallographic Data Center (CCDC) under deposition numbers 1936197 (**3aa**) and 1936198 (**7aa**). These data could be obtained free of charge from The Cambridge Crystallographic Data Center via http://www.ccdc.cam.ac.uk/data_request/cif.

## References

1. Brennfuehrer, A., Neumann, H. & Beller, M. Palladium-catalyzed carbonylation reactions of aryl halides and related compounds. *Angew. Chem. Int. Ed.* **48**, 4114–4133 (2009).
2. Liu, Q., Zhang, H. & Lei, A. Oxidative carbonylation reactions: organometallic compounds (R-M) or hydrocarbons (R-H) as nucleophiles. *Angew. Chem. Int. Ed.* **50**, 10788–10799 (2011).
3. Sumino, S., Fusano, A., Fukuyama, T. & Ryu, I. Carbonylation reactions of alkyl iodides through the interplay of carbon radicals and Pd catalysts. *Acc. Chem. Res.* **47**, 1563–1574 (2014).
4. Wu, X.-F. et al. Transition-metal-catalyzed carbonylation reactions of Olefins and alkynes: a personal account. *Acc. Chem. Res.* **47**, 1041–1053 (2014).
5. Wu, L. et al. Palladium-catalyzed carbonylative transformation of C(sp3)−X bonds. *ACS Catal.* **4**, 2977–2989 (2014).
6. Chen, J. et al. Base-controlled selectivity in the synthesis of linear and angular fused quinazolinones by a palladium-catalyzed carbonylation/nucleophilic aromatic substitution sequence. *Angew. Chem. Int. Ed.* **53**, 7579–7583 (2014).
7. Lin, M., Li, F., Jiao, L. & Yu, Z.-X. Rh(I)-catalyzed formal [5+1]/[2+2+1] cycloaddition of 1-Yne-vinylcyclopropanes and two CO units: one-step construction of multifunctional angular tricyclic 5/5/6 compounds. *J. Am. Chem. Soc.* **133**, 1690–1693 (2011).
8. Li, X., Song, W. & Tang, W. Rhodium-catalyzed tandem annulation and (5 +1) cycloaddition: 3-hydroxy-1,4-enyne as the 5-carbon component. *J. Am. Chem. Soc.* **135**, 16797–16800 (2013).
9. Cheng, J., Qi, X., Li, M., Chen, P. & Liu, G. Palladium-catalyzed intermolecular aminocarbonylation of alkenes: efficient access of β-amino acid derivatives. *J. Am. Chem. Soc.* **137**, 2480–2483 (2015).
10. Li, M., Yu, F., Qi, X., Chen, P. & Liu, G. Cooperative strategy for the highly selective intermolecular oxycarbonylation reaction of alkenes using a palladium catalyst. *Angew. Chem. Int. Ed.* **55**, 13843–13848 (2016).
11. Qi, X., Yu, F., Chen, P. & Liu, G. Palladium-catalyzed intermolecular oxidative fluorocarbonylation of unactivated alkenes: efficient access of β-fluorocarboxylic esters. *Angew. Chem. Int. Ed.* **56**, 12692–12696 (2017).
12. Ding, D., Zhu, G.-H. & Jiang, X.-F. Ligand controlled Pd(II)-catalyzed regiodivergent carbonylation of alkynes for syntheses of indolo[3,2-c] coumarins and benzofuro[3,2-c]quinolinones. *Angew. Chem. Int. Ed.* **57**, 9028–9032 (2018).
13. Wu, L.-J., Song, R.-J., Luo, S. & Li, J.-H. Palladium-catalyzed reductive [5+1] cycloaddition of 3-acetoxy-1,4-enynes with CO: access to phenols enabled by hydrosilanes. *Angew. Chem. Int. Ed.* **57**, 13308–13312 (2018).
14. Li, X., Chen, P. & Liu, G. Pd-catalyzed intermolecular arylcarbonylation of unactivated alkenes: incorporation of bulky aryls at room temperature. *Angew. Chem. Int. Ed.* **57**, 15871–15876 (2018).

15. Zheng, W.-F. et al. Tetrasubstituted allenes via the palladium-catalysed kinetic resolution of propargylic alcohols using a supporting ligand. *Nat. Catal.* **2**, 997–1005 (2019).

16. Yang, J. et al. Direct synthesis of adipic acid esters via palladium-catalyzed carbonylation of 1,3-dienes. *Science* **366**, 1514–1517 (2019).

17. Negishi, E.-i et al. Palladium-catalyzed carbonylative cyclization of 1-iodo-2-alkenylbenzenes. *J. Am. Chem. Soc.* **118**, 5904–5918 (1996).

18. Aggarwal, V. K., Davies, P. W. & Moss, W. O. A palladium catalysed cyclisation-carbonylation of bromodienes: control in carbonylation over facile β-hydride elimination. *Chem. Commun.* **9**, 972–973 (2002).

19. Seashore-Ludlow, B. & Somfai, P. Domino carbopalladation-carbonylation: generating quaternary stereocenters while controlling β-hydride elimination. *Org. Lett.* **12**, 3732–3735 (2010).

20. Seashore-Ludlow, B., Danielsson, J. & Somfai, P. Domino carbopalladation-carbonylation: investigation of substrate scope. *Adv. Synth. Catal.* **354**, 205–216 (2012).

21. Liu, X. & Gu, Z. Pd-catalyzed heck cyclization and in situ hydrocarboxylation or hydromethenylation via a hydrogen borrowing strategy. *Org. Chem. Front.* **2**, 778–782 (2015).

22. Gehrtz, P. H., Hirschbeck, V., Ciszek, B. & Fleischer, I. Carbonylations of alkenes in the total synthesis of natural compounds. *Synthesis* **48**, 1573–1596 (2016).

23. Bai, Y., Davis, D. C. & Dai, M. Natural product synthesis via palladium-catalyzed carbonylation. *J. Org. Chem.* **82**, 2319–2328 (2017).

24. Ma, K., Martin, B. S., Yin, X. & Dai, M. Natural product syntheses via carbonylative cyclizations. *Nat. Prod. Rep.* **36**, 174–219 (2019).

25. Artman, G. D. & Weinreb, S. M. An approach to the total synthesis of the marine ascidian metabolite perophoramidine via a halogen-selective tandem Heck/carbonylation strategy. *Org. Lett.* **5**, 1523–1526 (2003).

26. Bai, Y., Shen, X., Li, Y. & Dai, M. Total synthesis of (-)-spinosyn A via carbonylative macrolactonization. *J. Am. Chem. Soc.* **138**, 10838–10841 (2016).

27. Xu, L., Wang, C., Gao, Z. & Zhao, Y.-M. Total Synthesis of (±)-cephanolides B and C via a palladium-catalyzed cascade cyclization and late-stage sp3 C–H bond oxidation. *J. Am. Chem. Soc.* **140**, 5653–5658 (2018).

28. Ma, K., Yin, X. & Dai, M. Total syntheses of bisdehydroneostemoninine and bisdehydrostemoninine by catalytic carbonylative spirolactonization. *Angew. Chem. Int. Ed.* **57**, 15209–15212 (2018).

29. Han, A., Tao, Y. & Reisman, S. E. A 16-step synthesis of the isoryanodane diterpene (+)-perseanol. *Nature* **573**, 563–567 (2019).

30. Zanti, G. & Peeters, D. DFT study of small palladium clusters Pdn and their interaction with a CO ligand (n = 1–9). *Eur. J. Inorg. Chem.* **2009**, 3904–3911 (2009).

31. Noonan, G. M. et al. Regioselective and enantioselective hydroformylation of dialkylacrylamides. *Adv. Synth. Catal.* **352**, 1047–1054 (2010).

32. Carmona, R. C., Koster, O. D. & Duarte Correia, C. R. Chiral N,N ligands enabling palladium-catalyzed enantioselective intramolecular Heck-Matsuda carbonylation reactions by sequential migratory and CO insertions. *Angew. Chem. Int. Ed.* **57**, 12067–12070 (2018).

33. Hu, H. et al. Enantioselective synthesis of 2-oxindole spiro-fused lactones and lactams by Heck/carbonylative cyclization: method development and applications. *Angew. Chem. Int. Ed.* **58**, 9225–9229 (2019).

34. Cheng, C., Wan, B., Zhou, B., Gu, Y. & Zhang, Y. Enantioselective synthesis of quaternary 3,4-dihydroisoquinolinones via Heck carbonylation reactions: development and application to the synthesis of Minalrestat analogues. *Chem. Sci.* **10**, 9853–9858 (2019).

35. Filippini, M. H. & Rodriguez, J. Synthesis of functionalized bicyclo[3.2.1]octanes and their multiple uses in organic chemistry. *Chem. Rev.* **99**, 27–76 (1999).

36. Presset, M., Coquerel, Y. & Rodriguez, J. Syntheses and applications of functionalized bicyclo[3.2.1]octanes: thirteen years of progress. *Chem. Rev.* **113**, 525–595 (2013).

37. Bashore, C. G. et al. Enantioselective synthesis of nicotinic receptor probe 7,8-difluoro-1,2,3,4,5,6-hexahydro-1,5-methano-3-benzazocine. *Org. Lett.* **8**, 5947–5950 (2006).

38. Grachan, M. L., Tudge, M. T. & Jacobsen, E. N. Enantioselective catalytic carbonyl-ene cyclization reactions. *Angew. Chem. Int. Ed.* **47**, 1469–1472 (2008).

39. Rueping, M., Kuenkel, A., Tato, F. & Bats, J. W. Asymmetric organocatalytic domino Michael/Aldol reactions: enantioselective synthesis of chiral cycloheptanones, tetrahydrochromenones, and polyfunctionalized bicyclo-[3.2.1] octanes. *Angew. Chem. Int. Ed.* **48**, 3699–3702 (2009).

40. Huwyler, N. & Carreira, E. M. Total synthesis and stereochemical revision of the chlorinated sesquiterpene (±)-gomerone C. *Angew. Chem. Int. Ed.* **51**, 13066–13069 (2012).

41. Zhu, S., Zhang, Q., Chen, K. & Jiang, H. Synergistic catalysis: metal/proton-catalyzed cyclization of alkynones toward bicyclo[3.n.1]alkanones. *Angew. Chem. Int. Ed.* **54**, 9414–9418 (2015).

42. Ando, Y., Hori, S., Fukazawa, T., Ohmori, K. & Suzuki, K. Toward naphthocyclinones: doubly connected octaketide dimers with a bicyclo[3.2.1] octadienone core by thiolate-mediated cyclization. *Angew. Chem. Int. Ed.* **54**, 9650–9653 (2015).

43. Burns, A. R., Madec, A. G. E., Low, D. W., Roy, I. D. & Lam, H. W. Enantioselective synthesis of bicyclo[3.n.1]alkanes by chiral phosphoric acid-catalyzed desymmetrizing Michael cyclizations. *Chem. Sci.* **6**, 3550–3555 (2015).

44. Zhu, C., Wang, D., Zhao, Y., Sun, W.-Y. & Shi, Z. Enantioselective palladium-catalyzed intramolecular α-arylative desymmetrization of 1,3-diketones. *J. Am. Chem. Soc.* **139**, 16486–16489 (2017).

45. He, C., Hu, J., Wu, Y. & Ding, H. Total syntheses of highly oxidized ent-kaurenoids pharicin A, pharicinin B, 7-O-acetylpseurata C, and pseurata C: A [5+2] cascade approach. *J. Am. Chem. Soc.* **139**, 6098–6101 (2017).

46. Ramachary, D. B., Anif Pasha, M. & Thirupathi, G. Organocatalytic asymmetric formal [3+2] cycloaddition as a versatile platform to access methanobenzo[7]annulenes. *Angew. Chem. Int. Ed.* **56**, 12930–12934 (2017).

47. Zhao, L., Li, Z., Chang, L., Xu, J., Yao, H. & Wu, X. Efficient construction of fused indolines with a 2-quaternary center via an intramolecular Heck reaction with a low catalyst loading. *Org. Lett.* **14**, 2066–2069 (2012).

48. Su, Y., Zhou, H., Chen, J., Xu, J., Wu, X., Lin, A. & Yao, H. Solvent-controlled switchable C–H alkenylation of 4-aryl-1H-pyrrole-3-carboxylates: application to the total synthesis of (±)-rhazinilam. *Org. Lett.* **16**, 4884–4887 (2014).

49. Yuan, J., Feng, Z., Zeng, Y., Zhao, X., Lin, A. & Yao, H. Palladium-catalyzed asymmetric intramolecular reductive Heck desymmetrization of cyclopentenes: access to chiral bicyclo [3.2.1] octanes. *Angew. Chem. Int. Ed.* **58**, 2884–2888 (2019).

50. Han, C., Fu, Z., Guo, S., Fang, X., Lin, A. & Yao, H. Palladium-catalyzed remote 1,n-arylamination of unactivated terminal alkenes. *ACS Catal.* **9**, 4196–4202 (2019).

51. Watson, D. A., Fan, X. & Buchwald, S. L. Carbonylation of aryl chlorides with oxygen nucleophiles at atmospheric pressure. Preparation of phenyl esters as acyl Transfer agents and the direct preparation of alkyl esters and carboxylic acids. *J. Org. Chem.* **73**, 7096–7101 (2008).

52. Wu, X.-F., Neumann, H. & Beller, M. Convenient carbonylation of aryl bromides with phenols to form aryl esters by applying a palladium/di-1-adamantyl-n-butylphosphine catalyst. *ChemCatChem* **2**, 509–513 (2010).

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## Author contributions

Z.Y. planned and conducted most of the experiments; Z.Y., Y.Z., Z.F., and Z. G. prepared substrates for the reaction scope evaluation; A.L. and H.Y. directed the projects and cowrote the manuscript. All authors contributed to the discussion.

## Competing interests

The authors declare no competing interests.

## Additional information

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